DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE

OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

Thursday, June 28, 2001

8:25 a.m.

Advisors and Consultants Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Victor M. Santana, M.D., Chairman
Karen M. Templeton-Somers, Ph.D., Executive Secretary

MEMBER:

Donna Przepiorka, M.D., Ph.D.

AD HOC MEMBERS:

Susan L. Cohn, M.D.
Alice Ettinger, MSN, RN, CPON, CPNP
Jerry Z. Finklestein, M.D.
Henry S. Friedman, M.D.
C. Patrick Reynolds, M.D., Ph.D.

PATIENT ADVOCATES:

Nancy Keen
Susan L. Weiner, Ph.D.

CONSULTANTS:

Larry Kun, M.D.
David M. Parham, M.D.

GUESTS AND GUEST SPEAKERS:

Robert S. Benjamin,
Peter Burger, M.D.
Anthony Elias, M.D.
Howard A. Fine, M.D.
Amar Gajjar, M.D.
Stuart A. Grossman, M.D.
Frederic Kaye, M.D.
Victor A. Levin, M.D.
Michael P. Link, M.D.
Paul A. Meyers, M.D.
Roger Packer, M.D.
Elizabeth J. Perlman, M.D.
Scott L. Pomeroy, M.D.
David Poplack, M.D.
Malcolm Smith, M.D., Ph.D.
Susan M. Staugaitis, M.D., Ph.D.

FDA:

Richard Pazdur, M.D.
Steven Hirschfeld, M.D., Ph.D.
Joseph Gootenberg, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. SANTANA: Good morning. We are meeting this morning as part of the Pediatric Subcommittee of the Oncology Drugs Advisory Committee. This meeting was called by the agency to give them advice and guidance on issues related to pediatric development and, in particular, extrapolation of information from adult studies that could be relevant to pediatric studies as it applies to the agency's regulatory role and the Pediatric Rule.

We are going to go ahead and get started. The first item is to have Dr. Pazdur address the committee. Richard?

Welcome

DR. PAZDUR: Thank you very much. This is one of three meetings that we are having to look at the 1998 Pediatric Rule which, as Victor alluded to, allows for the extrapolation of adult data to the pediatric population. The first meeting looked at leukemia and lymphomas and, obviously, the nature of this meeting is looking at other malignancies, particularly sarcoma, lung and CNS malignancies and other solid tumors. Our third

meeting, which I believe is going to be held in September, or to be announced -- some of you may be asked to come back so we will get back to you with specific dates and your calendars -- will look at clinical trial design issues in pediatrics to address issues of extrapolation of data, etc. So, on behalf of the FDA, our Division of Oncology Drug Products and our colleagues at CBER who handle biologics, we would like to welcome you to this committee meeting and look forward to an ongoing dialogue with you. Thanks.

DR. SANTANA: Thanks, Richard. I want to go ahead and introduce the committee members. There are some people that are new to the meeting and, for the purposes of record-keeping, we need to state our name and affiliation. So, Stuart, can you get started from that side of the table please?

Introduction of the Committee

DR. GROSSMAN: Stuart Grossman, from Johns Hopkins University.

DR. LINK: Michael Link, from Stanford.

DR. MEYERS: Paul Meyers from Memorial Sloan-Kettering.

DR. PACKER: Roger Packer, Children's National Medical Center, Washington, D.C.

DR. POMEROY: Scott Pomeroy, Harvard Medical School.

DR. PAZDUR: Richard Pazdur, Oncology Division, FDA.

DR. HIRSCHFELD: Steven Hirschfeld, Oncology Division, CDER, FDA.

DR. GOOTENBERG: Joe Gootenberg, with Oncology at Biologics, CBER.

DR. PARHAM: David Parham, Arkansas Children's Hospital.

DR. KUN: Larry Kun, St. Jude Children's Research Hospital.

DR. COHN: Susan Cohn, Children's Memorial Hospital in Chicago.

DR. ETTINGER: Alice Ettinger, St. Peter's University Hospital, New Brunswick, New Jersey.

DR. FRIEDMAN: Henry Friedman, Duke.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the ODAC, FDA.

DR. SANTANA: Victor Santana, St. Jude Children's Research Hospital.

DR. FINKLESTEIN: Jerry Finklestein, Long Beach Memorial, UCLA.

DR. PRZEPIORKA: Donna Przepiorka, Baylor, Houston.

DR. REYNOLDS: Patrick Reynolds, Children's Hospital, Los Angeles.

DR. WEINER: I am Susan Weiner. I am the patient advocate from The Children's Cause.

DR. LEVIN: Victor Levin, Department of Neuro-Oncology, M.D. Anderson Cancer Center.

DR. ELIAS: Anthony Elias, University of Colorado.

DR. BENJAMIN: Bob Benjamin, M.D. Anderson.

DR. GAJJAR: Amar Gajjar, St. Jude Children's Research Hospital.

DR. PERLMAN: Elizabeth Perlman, Johns Hopkins University.

DR. POPLACK: David Poplack, Baylor College of Medicine.

DR. SMITH: Malcolm Smith, National Cancer Institute.

DR. STAUGAITIS: Susan Staugaitis, Cleveland Clinic Foundation.

DR. FINE: Howard Fine, Neuro-Oncology Branch, NIH.

DR. SANTANA: That is it. Thank you so much. We have to read a conflict of interest statement. So, Karen, can you please proceed with

that?

Conflict of Interest

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Since the issues to be discussed by the subcommittee at this meeting will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to an entire class of products, in accordance with 18 U.S.C. Section 208(b), waivers have been granted to all members and consultants who have reported interests in any pharmaceutical companies.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Victor Levin, M.D., would like to disclose

that his retirement fund holds stock in Amgen, Bristol Myers Squibb, Merck, Alza, Pfizer and Pharmacia Corporation. Dr. Levin is also the Program Director of an NIH, NCI National Cooperative Drug Discovery Group grant, "Development of Drug Inhibitors of Src" and he is the Program Director of an NIH, NCI grant "Gliomas: Biologic, Molecular and Genetic Studies." He is also on the scientific advisory boards of Direct Therapeutics, Signase and Oncology Services Corporation. None of the companies he consults with have anticancer drugs in clinical trials except Direct Therapeutics, Inc. Dr. Levin is also the founder and current member of the Board of Directors of Signase, Inc. Lastly, his son is employed by Alza Pharmaceuticals.

Susan Staugaitis, M.D. would like to disclose that she owns stock in American Home Products, Bristol Myers Squibb and various mutual funds that may have investments in pharmaceutical firms.

Paul Meyers, M.D. is the principal investigator on a Bristol Myers Squibb sponsored Phase I study of Irinotecan in children with recurrent solid tumor. Dr. Meyers is also a

co-investigator for an Ortho-Biotech sponsored study of erythropoietin in children with solid tumors. Lastly, he is the principal investigator on a Genentech sponsored study of Trastuzumab for recurrent osteosarcoma.

Amar Gajjar, M.D. has a grant from Schering Plough.

Anthony Elias, M.D. would like to disclose that he is a researcher on clinical trials sponsored by Eli Lilly, Pharmacia and Ribozyme Pharmaceuticals.

Robert Benjamin, M.D. has received consulting fees from Bristol Myers Squibb, Nexstar and Sequus. He has also received speaker fees from Bristol Myers Squibb.

Lastly, David Poplack, M.D. would like to disclose that he has previously received speaker fees from Chiron and he is an unpaid scientific advisor to ASTA Corporation.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or pervious involvement with any firm whose products they may wish to comment upon. Thank you.

DR. SANTANA: Thanks, Karen. Any other committee members that want to make any comments regarding their conflict of interest?

[No response]

Thank you. We have some time now allocated for an open public hearing. Anybody in the audience that wishes to address the committee, this is the time to do so. If you want to address the committee, please come to the podium and state your name and your affiliation. Nobody from the audience wants to talk to us. Okay, thank you.

We are going to go ahead and start the meeting. The first item on the agenda is Steven Hirschfeld who will present the charge to the committee. Steven has been a major force at the FDA in trying to understand the issues of the Pediatric Rule as it relates to oncology. So, I want to thank Steven for all his efforts on behalf of the pediatric oncology community. Steven?

Charge to the Committee

DR. HIRSCHFELD: Thank you, and I want to thank and commend Dr. Santana for being the initial, first and unprecedented chair for this committee and for guiding it through its first year.

DR. SANTANA: And hopefully not the last!

DR. HIRSCHFELD: Right!

[Slide]

Pediatrics has been a driving force for changes in healthcare and particularly in clinical investigations. The major regulatory initiatives of this century were in reaction to pediatric-driven events. It was the morphine poisonings in the turn of the 19th to the 20th century. It was the alfa-nilomide-tainting scandal which led to the Food, Drug and Cosmetic Act, and then the amendments to the Food, Drug and Cosmetic Act which resulted in establishing the three principles that we use for regulatory science which is labeling, safety and efficacy which occurred in 1962 as a reaction to the malformations that were caused by thalidomide.

In addition, children have had a key role in the development of clinical investigations, and most particularly in oncology. The first

chemotherapy studies were done at first in uncontrolled studies in children and then in controlled studies. The formation of the National Cancer Institute and its clinical branches initially had studies which examined the roles of chemotherapy and also of statistics and of randomized controlled study design in children with leukemia. The advent of adjuvant therapy was first done in children.

Yet, despite all the contributions toward the development of clinical research and regulatory efforts, there has never been a robust therapeutic development program in children. So, there are some efforts that were initiated over the course of the last century but most explicitly in the last decade to try to remedy what many felt was an unjust situation.

We recognize that there are therapies that were administered to children without adequate study, both in general and in specific instances which relate to oncology. We recognize the extraordinary efforts of the cooperative groups in developing clinical protocols, and the extraordinary track record of both enrollment and of scientific progress. Nevertheless, many of the

treatments that are used have been difficult to come by, and many of the supportive care measures have never been studied in the types of environments which we would consider to be ideal, and we would strive for this ideal. We also note that many therapies are not made available for pediatric study until adult marketing studies or at least the adult program is well under way.

[Slide]

So, we have here a paradigm where the conventional and historical method is that preclinical studies with a new drug or biological lead to clinical trials in adults, and then following the adult development sometimes unintended, sometimes intended, sometimes as an afterthought comes pediatric development. What we would like to engender is a new paradigm where preclinical or non-clinical studies could lead to either simultaneous adult and pediatric development, or for those particular instances where there is an unmet medical need and there is a scientific basis for proceeding where studies can lead to therapeutic development in children and then, if applicable, for adults.

These inter-relationships is what we are

trying to explore in this committee over the course of the past year, looking at where we can form a matrix rather than a linear development plan.

[Slide]

The FDA, in the 1990's, attempted to facilitate the availability of drugs for study in children, and by drugs I mean drugs and biologicals. With the Rule in 1994 that attempted to ease the burden of clinical studies by allowing extrapolation of efficacy data from adult populations to pediatric populations certain conditions were met.

The conditions were, in brief, that the indication, which means the disease or condition, but that the indication is similar in adults and children and that the mode of action of the intended therapy is considered similar in adults and children. Therefore, the burden for scientific studies would rely on study designs which could establish appropriate dosing and appropriate safety information but would not necessarily have to recapitulate efficacy data.

This program was not the success it was intended to be. So, two other programs were initiated to replace it. The first was an

incentive program, which was part of the 1997 Food and Drug Administration Modernization Act, which offered a financial incentive to companies that were willing to pursue pediatric studies in response to a written request from the FDA. We recognize the FDA does not have the resources nor necessarily the wisdom to know which types of studies to request so a mechanism was developed to allow companies or interested third parties to propose to the FDA pediatric studies, which then the FDA would evaluate and then amend or issue a written request on the basis of that proposal.

This program has been highly successful. More pediatric studies have been initiated in the past five years than ever in the history of clinical investigations. This program has also resulted in the issuance of twenty written requests for pediatric oncology.

[Slide]

The other regulatory initiative is a mandate, and the mandate states that if the indication for an application under review can be found in children -- and the operative words here are "indication" and "under review" -- then the FDA can mandate -- and again the operative word is

"can" -- mandate pediatric studies. It applies to drugs and biologicals. If the indication does not apply to children or there are other compelling reasons not to pursue studies in children, then a waiver can be granted.

This rule does not specifically address the issue of extrapolation of efficacy. What this rule asks and what I ask this committee to bear in mind today is are studies warranted. Is there a scientific basis for considering pediatric studies?

I should also note that this rule is not intended nor has it ever, and we hope ever a situation would arise where a question comes, should it delay development for an adult indication because pediatric studies can always be deferred and there is no intent to ever delay the availability or marketing of a new therapy for adults.

[Slide]

So, the specific question we would like to ask the committee this morning and this afternoon is how should this rule be applied for solid tumors and central nervous system malignancies.

[Slide]

What we would hope is that by the end of

the day we could have some recommendations for adult indications that should trigger the Pediatric Rule; some specific recommendations for adult indications that should be waived from compliance with the Pediatric Rule; and when this rule was written we anticipated the situation, and there are circumstances such as breast cancer where the disease does not occur in children or occur in sufficient numbers that an examination is warranted every time an application is under review, there is an automatic waiver. So, our question is should there be other such conditions?

We would like, lastly, recommendations for general principles that may be used to apply the Pediatric Rule. We recognize that classification schema are always changing, are fluid, as they should be, and rather than convene a committee on a regular basis to generate lists to update, it would be helpful and preferable if we could have some principles articulated to help us apply and interpret the rule. Thank you.

Challenges and Considerations in Linking Adult and Pediatric Solid Tumors

DR. SANTANA: We will go ahead and do the presentations and we will have plenty of time for

questions and discussion to kind of keep it moving. I am going to go ahead and take the podium.

[Slide]

What I want to do in the next ten minutes or so is not to review all the challenges and indications that may relate to pediatric solid tumors but actually when I was thinking about doing this what I decided to do were two things. One is to kind of give a general overview consensus of what I have taken out of the past couple of discussions of this committee and my understanding of where pediatric research and FDA regulatory issues converge. Then, lastly, I would like to bring forth the two points that to me are critical as we move forward in considering extrapolation of data, the two questions that we should always ask when we are faced with that challenge. So, hopefully, in the next ten minutes I will be able to cover all that.

[Slide]

Clearly, there are two major issues here. One is the research implications and the other one is the regulatory implications, and by regulatory implications I am only focusing on the FDA perspective as it relates to the Pediatric Rule.

[Slide]

I think these are really a continuum, and I think in pediatrics, and particularly in pediatric oncology, we have a major advantage in that pediatric oncology practice really occurs almost exclusively within the research setting and research trials are really the standard of care for children in the United States who have cancer. This is in real contrast to what happens in adult oncology in which this is not the case or what may happen in other pediatric diseases that are not oncology in which research trials are not the primary driving force of how patients are taken care of.

From the regulatory perspective, once again just focusing on the comment of how it relates to the FDA and the Pediatric Rule, I think we have to remember that the FDA is always looking and the sponsors are always presenting data to the agency in support of indications. I mean, that is the ultimate goal of why they come to the agency. In support of indications, obviously, they are interested in looking at issues of efficacy as an important endpoint but, as Steven addressed a little bit earlier, a major component relates to

issues of safety and most of the mishaps that have occurred in pediatric regulatory issues have actually been issues related to safety and I am going to talk a little bit about that later in regards to some of the oncology drugs and how we may address those.

I think whatever sponsors and the FDA do with indications ultimately influences medical practice not only in adults but also to a certain degree in pediatrics, although in pediatric oncology the ongoing theme is always that it is done in the setting of research.

[Slide]

Now, I think we have to recognize that there are some major limitations in pediatrics. One is that we have a limited patient population. So, many of the questions that we would like to address many times cannot be addressed because there is a limiting factor in terms of the number of patients. A corollary to that is that many of the diseases and solid tumors, for example, that we treat are very heterogeneous in nature and there are not large populations of patients within one tumor category in which we can ask many different questions. So, this is very different if you look

at it from the adult perspective because from the adult perspective, in terms of drug development, there are many agents that can be tested in a Phase I setting because there are many adults in terms of the numbers that can help us address those questions.

Secondly, there are even fewer new agents that can be evaluated in Phase II trials in children because of the historical notion that many trials first had to be conducted in adults before any studies could be conducted in children. As Malcolm Smith has reminded us many times, for many of the pediatric solid tumors we can realistically only do a Phase III study every four or five years because of the issues of number of patients and the issues of which are the real important questions that have to be answered. I think the example there is what has happened with Ewing's sarcoma and osteosarcoma in the last decade in which realistically, at the national level, Phase III studies in those tumor types could only be carried on in the context of every four to five years. I think that is important as, from the research perspective, we try to address what are the real questions that we should be asking.

So, from the research perspective there need to be mechanisms by which we can prioritize what we can do in pediatric oncology with our trials, and I think these three points that Malcolm Smith has expressed before are that these prioritizations have to be based on some idea of a successful approach in adults because of the issue of the limitation of patient numbers; that there be compelling preclinical rationales for why these questions with these agents should be asked in children; and then paying some close attention to the patient population at hand because there may be specific patient populations in pediatric oncology in which this may be more reasonable. For example, patients at high risk for recurrence provide a unique mechanism for us to be able to ask some of these research questions.

[Slide]

However, as Steven addressed this a little bit earlier, one of the primary concerns always in pediatric research is this issue that we have to obtain useful data. It is going to be limited data, and a central issue is always the issue of safety in children. None of us wants to be involved with issues in which an agent, even in a

research setting or a regulatory setting, has had children involved and major mishaps occur. I think it not only presents issues of our relationship with the community but also from an ethical point. We want to make sure that what we do with children is always safe.

So, I think we have to recognize that there always have to be studies done in children with new agents to help us understand whether the MTD, the pharmacokinetics and the pharmacodynamics are truly different so that when these agents then become publicly available we don't have issues with safety.

The two that I have outlined here are good examples. As you know, Taxol is not a drug that we use a lot in solid tumors or in pediatric oncology, but the schedules of administration of Taxol are really very different in adults versus children, and that relates primarily to the vehicles in which this drug was originally formulated and the toxicity that the vehicle may present when it is given to children in very short infusions.

Similarly, teniposide, where the vehicle preparation has a lot of alcohol in it, one has to be very careful with high doses of teniposide in

children because potentially issues of alcohol toxicity may be related to the safety in use of this drug.

So, the point here is just to present to you two very brief examples of how we cannot technically extrapolate all the adult data in terms of pharmacokinetics and dynamics to children because there may be particular issues with children that have to be addressed in the safety issue.

Then, lastly -- I don't want to beleaguer this point of safety but we have to recognize that there are different populations and even babies are different from ten-year olds and fifteen-year olds as relates to the metabolism of drugs.

[Slide]

So, the question that we have for us today that Steven presented, under the auspices of this Pediatric Rule, how do we consider whether solid tumors in adults and children are either similar or different, and why is it important to us and why are we here?

Well, I think the first point is that there are truly limited opportunities to test new agents in children so we have to be very careful in

what we bring forward.

We have to make this regulatory mandate very practical. I think Steven was hinting at that. We have to be careful that, from our business partners in the pharmaceutical industry, that we don't ask them to do things that are unrealistic and impractical. We have to make this mandate very practical for the benefit of us in the research community, for the benefit of our patients, and certainly for the benefit of the industry. This has to be done in a very practical way to make these agents then available for children.

I think you are going to hear a little bit of discussion today from various other presenters about ways in which potentially we can address this question of extrapolation of data by looking at phenotype. I am a believer that an osteosarcoma in a 10-year old is the same thing as an osteosarcoma in a 25-year old. Maybe somebody believes differently. We will hear that maybe today.

We could look at it from the genotypic point of view, from the molecular point of view. There may be common genotypes or molecular events that make us believe that tumors are very similar

although histologically they may be very different.

[Slide]

So, my two rules then in trying to answer this question are what two things am I going to be looking for to help me decide whether things are different or are similar enough that I could consider them the same? I think in that regard the two points that I hope we will hear some discussion today of are, first of all, looking at the biology, are there differences and similarities in the biology? That is, what creates the disease phenotype? If that is similar enough, are we really talking about the same disease and the same manifestations?

The second point is that as we try to extrapolate data we need to look at the host, and we need to look at differences and similarities in the host because that may be critical in terms of determining drug metabolism and toxicity and relating to issues of safety, which is obviously a primary concern.

[Slide]

Lastly, I want to present to you kind of a general outline of how we may consider some of these points in terms of extrapolating both the

biology and in terms of extrapolating host factors. The progression and the malignant transformation for the same tumor type may be very similar or may be very different in children versus adults. There may be common elements, such as drug resistance, that tell us that the disease clinically behaves the same way. Or, there may be differences in host factors and enzyme polymorphisms that may lead us to believe that, from the safety perspective, this is an issue that we need to address in a different population by looking at different pediatric populations in a very unique way.

So, I wanted to finish here by just giving you my perspective on this issue in a very general sense. My intent was not to discuss every single solid tumor and the challenges and implications of that because I think that will be done later today by other speakers. Thank you. Henry?

Challenges and Considerations in Linking Adult and Pediatric CNS Malignancies

DR. FRIEDMAN: This is a special day for me since I have never done power-point before and I want someone to come up and show me something, and to be sure this went well I sent the slides ahead to Karen and to Steve, the FDA, living and dead,

Congress and the District of Columbia. So, there are a lot of slides that are out there.

[Laughter]

DR. SANTANA: Remember, Henry, that everything you say here will be in the public record. Okay?

DR. FRIEDMAN: I always remember that! I strive for that!

[Slide]

What I am going to try to do today is to show some of the challenges and considerations involved in linking adult and pediatric CNS tumors.

[Slide]

The question posed is what is the relationship between adult and pediatric CNS tumors? Are there compelling similarities or differences in these tumors which can guide us in the application of the Pediatric Rule of 1998?

[Slide]

This shows you the histologic classification of tumors of the CNS taken from the most recent WHO publication. You can see that tumors are divided into neuroepithelial tissues, astrocytic, oligodendroglial, mixed glioma and embryonal, ependymal, choroid-plexus, neuronal and

mixed neuronal tumors and pineal parenchymal tumors --

[Slide]

-- continuing with meningeal tumors, primary CNS lymphomas, germ cell, tumors of the sellar region and metastatic tumors. So, the real question is what is the difference in the adult and pediatric population?

[Slide]

First off, malignant gliomas, meningiomas, Schwann cell and pituitary tumors are the most common tumors we see in the adult population as opposed to benign gliomas, medulloblastomas/PNETs, which is primitive neuroepidermal tumor, and craniopharyngiomas which are the most common in the pediatric population.

[Slide]

The vast majority of adult tumors are in the cerebral hemispheres. In pediatrics more than 50 percent of tumors in children who are over a year in age are infratentorial, but a majority of tumors in children less than one year of age are also supratentorial but they are different from the adult tumors -- the chiasmatic-hypothalamic gliomas and choroid plexus tumors.

[Slide]

So, are they differences between adult and pediatric non-glial CNS tumors -- the neuroepithelial, nerve sheath, meningeal, germ cell, CNS lymphoma, sellar tumors? The bottom line is that there is no compelling data which suggests that there is a meaningful difference between these tumors in adults and children. There may be differences but at the biological level there is no compelling data to say there is a difference.

[Slide]

Are there differences between adult and pediatric gliomas -- ependymomas, pilocytic astrocytoma, oligodendroglioma, subependymoma, diffuse fibrillary astrocytoma? Again, no data supports a meaningful, if any, difference between these tumors in adults and children. I want to acknowledge Peter Burger's help in looking at some of these issues. He was very helpful in our discussions.

[Slide]

So, we really resolve to are there differences between adult and pediatric malignant astrocytomas -- the anaplastic astrocytomas, the glioblastoma multiforme?

[Slide]

This is taken from a number of different sources, one of David Lewis' publications most recently, showing you a number of the molecular changes that occur in the development of a pilocytic astrocytoma, the so-called secondary glioblastoma multiforme and the primary glioblastoma multiforme which has a hallmark of EGFR gene amplification. But, again, how does this help us with pediatric versus adult? You have copies of all these slides.

[Slide]

So, a series of questions, the same question slide after slide now: are there molecular distinctions between adult and pediatric malignant astrocytoma? Rickert et al., in American Journal of Pathology, 2001, compared adult tumors. Plus 1P, plus 2Q, plus 21Q, minus 6Q, minus 11Q, and minus 16Q were more frequent in pediatric malignant glioma than in adult malignant glioma.

[Slide]

Sung, et al., in Brain Pathology, 2000, pediatric malignant astrocytoma show a preferential p53 pathway inactivation, 95 percent or more, moderate RB pathway inactivation, 25 percent, and

no EGFR amplification.

[Slide]

Cheng, in Human Pathology, '99, pediatric malignant gliomas have moderate rates of p53 mutation, a lack of EGFR amplification, a low rate of PTEN mutation, and a moderate rate of microsatelite instability as opposed to adult tumors.

[Slide]

Pediatric malignant astrocytomas rarely display EGFR amplification but frequently display increased EGFR expression, from Bredel, et al., in Clinical Cancer Research.

[Slide]

Pollock showed malignant astrocytomas in children greater than four years of age display TP53 mutations and p53 overexpression similar to adult tumors. Both TP53 mutations and p53 overexpression were much lower in children less than four years of age, showing a difference in the true biology of older and younger children.

[Slide]

Again, malignant astrocytomas are more similar than distinct in adults versus children greater than four years of age. So, in the older

child, although there are obviously distinctions in their molecular phenotype or molecular expression of genes, the similarities are greater than the distinctions.

[Slide]

I would like to modify this slide a bit. The Pediatric Rule applies to all adult brain tumors, including malignant astrocytoma, however, as we have started to hear and will continue to hear, the number of tumors in pediatrics -- the resources are so limited that it is going to be key that there not be just a reflex application of the Pediatric Rule to any adult brain tumor, but that a discussion with the representative groups that are addressing this problem be held on a tumor by tumor or trial by trial basis to make a decision whether it is appropriate to actually extend the rule and enforce it.

[Slide]

Advantages -- and I want to thank Steve Hirschfeld for help with this -- to joint adult and pediatric malignant gliomas, new and improved therapies for the patients; a better understanding of the biology of the diseases; development of common, comprehensive prospective biological

studies; a better understanding of the effects of therapy in poor and good prognosis groups; new study paradigms; more efficient study accrual and use of resources.

[Slide]

However, we may be making some assumptions that are in error in children exposed to therapies of no merit. There is always the concern of adverse events in children having a greater pebble in the pond effect than in the adult population -- just intrinsically the way this country operates. Requirement for cooperation and sharing of resources may delay or confound study implementation. I think the merger of POD and CCG has formed one central organization. There is also the Pediatric Brain Tumor Consortium. More groups mean more committees; more committees means more time, not necessarily time well spent. Potential need for complex stratification and analysis.

But the bottom line is that we have an opportunity when the situation is appropriate to take advantage of the Pediatric Rule because I don't believe, and we will see how the discussion goes today, that we will see a situation where we want to apply the rule and we don't have grounds to

apply the rule. Thank you.

Discussion

DR. SANTANA: Thanks, Henry. We now have time for discussion of the three prior speakers if anybody has any questions to Steven, to Henry or myself or want to make any general comments about where we are so far. Paul?

DR. MEYERS: Henry, I think you made a very compelling case that the biology is strongly in favor of linking the pediatric and adult brain tumors, but you didn't address the issue of toxicity and whether or not you think there are specific toxicities for brain tumor treatment that would impede that ability.

The other question I would like to ask you is are there any clinical differences in the behavior of these tumors? I recognize we should all be looking at biology as the more fundamental question but, for example, do these tumors progress more rapidly in children and does that have an implication for clinical trial design?

DR. FRIEDMAN: In terms of the second question first, I don't know how to answer that because therapies are so distinct that the clinical course of the tumors is obviously going to be

influenced by the interventions you use, and the approaches in the adult and the pediatric population are frequently quite disparate. So, it is hard to answer that question. I will turn it over to others -- Roger perhaps -- in a second.

The first question, certainly, I think the toxicities are going to be an issue. If there is going to be an adult trial which is going to use 50,000 sonograde whole brain radiotherapy, perhaps in pediatrics we might frown upon that kind of a study. I am only kidding, folks; we are not going to do that. But, certainly, there are going to be situations where, because of the developing CNS, we might be eager to avoid certain interventions.

If you are talking about things that have unclear neurotoxicity, that will have to be factored in. I mean, certainly if there are interventions which you know are going to pose more risk of damage and you know you have a more vulnerable situation in the pediatric population, you are going to have to think about it. That is part of the rationale for a case by case type of situation, or tumor by tumor.

DR. MEYERS: I guess what I am suggesting is that Steve was looking to us to try to draw

general principles, and I am almost hearing from you that you think that is unlikely to be a possibility. You are really suggesting that we are going to need to look at each of these agents individually.

DR. FRIEDMAN: Correct, absolutely correct. Roger?

DR. PACKER: I really want to comment mainly on the second point. I think that one of the mistakes potentially made is that there has been a tremendous reservation to look at new agents in pediatric brain tumors because of the potential effects on the developing nervous system. There are ways now to monitor those effects, to evaluate them. There are certainly tumors for which we have really very little to offer patients. We are really hung up often by not being able to look at those agents. If we monitor them appropriately -- we have MRI; we have neuro-cognitive assessments; we have ways to monitor toxicity -- it shouldn't be the rate limiter to applying the rule, there may just have to be better considerations for how you evaluate toxicity.

The other component of that is that it is a true marketing issue for many of the companies.

If they get into a toxicity that may delay the drug getting to market, that is the major limitation. And, as we are looking at the new drugs we are not only looking at chemotherapies, we are looking at biologics, we don't know how turning on and off these genes is going to affect the development of the nervous system. We are looking at new drug delivery methods -- convection delivery for CNS tumors, and we are worried about the volume of the brain. There is always this tremendous difficulty to get over the barrier as we work with new companies, pharmaceutical firms, etc., of trying to get them to apply these to pediatrics.

I don't have the answer, except I think sometimes it is overblown where the damage is going to be. If there is going to be damage it will identify it if we choose the target population appropriately in those children who have no other options, which is where I think these things should be started, then I think the issue of CNS damage, though an important one, is often a secondary one.

DR. ELIAS: I just have a comment on something Victor said, and that is that basically we are talking really about Phase II/Phase III type of indications. It is clear from your discussion

that Phase I cannot be bypassed. The pediatric populations are sufficiently different in a variety of way the PK, growth of the organism, and so forth -- that you really cannot bypass the safety considerations. But what we are really talking about in terms of the Pediatric Rule, I believe, would be the Phase II/III indications for market basically.

But I also agree that the safety issues represent a major stumbling block in terms of developing drugs, new agents. None of the pharmaceutical companies want toxicities associated with their agent.

DR. HIRSCHFELD: I will make a comment, and these are just general comments, and I will also invite Dr. Pazdur to follow up if he wishes. But I cannot think of a single example of the 85-plus drugs that we have approved where toxicity has proved to be the stumbling block. It is always the issue of potential benefit versus potential risk. I think it is clear that we have put an enormous number of highly toxic substances out on the market -- not us per se, I mean the pharmaceutical industry and the academic investigators and everyone, but we have allowed

these products to be on the market despite, in some cases, their substantial toxicities because there is a perceived benefit that, at least based on the available data, seems to outweigh the potential risks. It is one of the reasons why there are medical oncologists and pediatric oncologists, because we require that there be physicians and facilities which specialize in the treatment and monitoring of the patients in order to administer these therapies.

The other issue that I wanted to comment on in terms of general points is that while we may not have specific principles, I think that if we would look for patterns, and I think by the end of the day we may see some emerge, we should keep our minds open as to what potentially may evolve. Dr. Pazdur, did you want to comment?

DR. PAZDUR: Basically, if you take a look at why NDAs do not get approved, it is not because of toxicity but because of lack of efficacy, by and large. The toxicity issues are usually answered well in advance to the time they get into an NDA situation as far as major toxicities. Unusual toxicities, especially if they occur in a pediatric population, could be handled in labeling

considerations or in further studies.

But this kind of fear that the FDA will halt the development of a drug because we see an unusual toxicity in a subpopulation I think may be somewhat overblown. Yes, we are interested in the toxicity. It may require further studies, but a lot of that could be handled in labeling issues or in really looking at the toxicities in subpopulations. The major issue or approval or non-approval of NDAs is not toxicity; it is the lack of efficacy, and I think a sponsor should be well aware of that.

DR. FINE: I think the only caveat I would say in speaking about brain tumors in particular, and later on in the afternoon I am going to address some of the clinical differences between the pediatric brain tumors and adult brain tumors, but I think it is important to say that efficacy can be defined, obviously, in very many different ways and particularly for adult brain tumors, where we are dealing mostly with malignant gliomas where the prognosis is so poor and our therapeutic interventions are so limited, we are more likely to approve a drug with marginal benefit and with issues of long-term toxicity hardly being an issue.

However, taking pediatric tumors as a whole, and we will talk about the specifics as the day goes on, generally, thank God, children tend to do better as a whole than the adults, maybe not per high grade tumor but as a whole. So, for a marginal benefit, if there is some significant long-term toxicity we may be more reticent to approve that drug for a pediatric indication than for an adult. I think that is the one caveat I would say.

DR. FINKLESTEIN: I think our challenge is to think out of the box, and thinking out of the box and going back to the history probably of the generation of this committee, the idea was how can we bring new ideas, new agents, new drugs to the pediatric population earlier so the lag time would be shortened? Dr. Hirschfeld referred to that in terms of the algorithms that he was showing.

So, I would prefer that we not discuss or not use the phrase we are only considering Phase II/Phase III studies. What we are considering and what our challenge is, as I understand it, is bringing the pediatric oncologic challenge to the forefront and thinking of a different way of getting our children to have an opportunity to get

new agents earlier on, and the contributions of Henry are excellent because by thinking together in a unison manner in terms of brain tumors this will help us. Now, I understand there have to be some exceptions, but I would really hope we will think out of the box and not think of the old algorithm because that is what we really want to get away from.

DR. PRZEPIORKA: A question for Steven. Victor and Henry both highlighted the fact that these tumors are not real prevalent in the pediatric population. Can you bring us up to date on what the FDA is doing to logistically identify the priorities within the pediatric oncology community for drugs in pediatric solid tumors and CNS malignancies?

DR. SANTANA: Maybe Malcolm will want to comment.

DR. HIRSCHFELD: I will refer to Malcolm but I will start by saying we wish we were in the position of having to prioritize these, but we are not. So, we are looking prospectively and hopefully at the circumstances.

I will just make one more point and then I will ask Dr. Malcolm Smith, who has taken a

leadership role in this arena, to address your question in more detail. But the other general point is that the '98 rule mandates that the drug be made available for studies, or the biological. It doesn't say it should be approved for children. It doesn't say that it should be in any other way disseminated but should be in a controlled circumstance, made available for studies, and that was the principle I wanted to emphasize. Can I just turn it over to Dr. Smith?

DR. SMITH: I would emphasize some of what Victor said, that there is the need for prioritization. In terms of the prioritization process, I think it needs to lay with the experts in the pediatric cancers. So, we are trying to facilitate the prioritization process through the Children's Oncology Group and its Phase I Consortium; through the Pediatric Brain Tumor Consortium; through the disease committees of the Children's Oncology Group. We think that is where the prioritization needs to occur.

The kind of tools for prioritization -- and again Victor mentioned some of these, you know, if an agent looks super in an adult carcinoma maybe it is good in a pediatric embryonal tumor. It is a

good question. But we are trying to develop ways for prioritizing better, having additional data to base some of these decisions about whether the best drug for rhabdomyosarcoma is going to be a rhabdomycin analog or proteose inhibitor or an epidermal growth factor, etc., inhibitor or, you know, SDI571, all of which are either in the clinic in pediatrics or soon will be. So, we get to the point Victor was making, how many of those will we be able to study in Phase II in rhabdomyosarcoma or osteosarcoma? Then, which of those will we select to be our Phase III drug for the next four or five years, the question of therapy that we are asking?

We are tying to work with the pediatric research community to develop additional ways of using preclinical data to inform those decisions. We sponsored a meeting together with the Children's Oncology Group Phase I Consortium yesterday to begin assessing what tools there are available now for preclinical models, and then how those tools might be used in a more systematic way. I think that will be a key component to the prioritization process, and making more information available to the people making the decisions in the Phase I Consortium, the Brain Tumor Consortium, the disease

committees within COG.

DR. SANTANA: I want to take the chairman's prerogative and ask anybody in the audience from the pharmaceutical industry who wants to comment on these issues, because I think we are having a discussion here from the academic centers and from the regulatory agencies but the third point here in the triad is the business and pharmaceutical. So, I know there are a couple of representatives here and so I would invite anyone from the industry who is here who wants to comment on this particular issue to come to the podium. Please take the invitation. You don't get many opportunities. I will give you a couple of minutes to get your thoughts together.

DR. HIRSCHFELD: I just want to make one other clarifying comment on the general principles, and this applies to both the Pediatric Exclusivity Initiative and the Pediatric Rule. What we are attempting to facilitate is the generation of information, data, as it relates to pediatrics. So, in the Pediatric Exclusivity program we are willing to give a financial incentive for even negative data because we consider it important that there be credible data available for study in

children. The same with the Pediatric Rule, even if the drug does not lead to approval or leads to an indication, it will still provide useful data.

The mechanism that we have for disseminating the useful data is in the product label, and we would consider it an effort well worth the undertaking if we were able to write information which was of use to practitioners in a product label, again, even if it didn't lead to an indication.

DR. SANTANA: Roger?

DR. PACKER: A comment and then a question to the committee. The comment is I am not absolutely sure that prioritization is not an issue. We have already run into the road blocks in some of the new angiogenesis and biology drugs of how we are going to prioritize those drugs and how we are going to apply them to pediatrics. We have also hit road blocks at the regulatory level, at the government regulatory level of allowing those drugs to go into pediatric trials for pediatric brain tumors until there is some adult data showing their efficacy, which is a real problem in some of the things. I don't want to go into specifics but just to say that at the regulatory level it isn't

all that black and white, that there are road blocks at this point.

The question to the committee though is that I understand, I think, fairly well how this rule is applied in one direction and it hasn't been that difficult for many of the investigators here to take a drug in adult malignant gliomas and apply it to pediatric malignant gliomas. I think the drug companies understand that the regulatory agencies understand it. Where I have difficulty is how is this drug or biologic going to be applied for tumors where there is not a tremendous interest in adult trials? How are we going to apply it where there aren't drug trials for low grade gliomas, which is a major pediatric problem? Whether or not drug trials for primitive neuroectodermal tumors in adults, which is a major pediatric problem -- what data will be utilized by the FDA to make this rule apply to those tumors that are not in trials in adults?

DR. LEVIN: I would like to expand on that just a bit and clarify one aspect of it, and that is that the same problems exist in the adult groups for treating anaplastic astrocytomas because getting access to new drugs is basically focused on

the fast market approach of looking at glioblastoma and for many of these new drugs that is not the target. The target is a much lower grade tumor. So, we have the same problems that you do in addressing anaplastic tumors and lower grade astrocytic tumors.

I would like to make one more comment and maybe put it in a different light, and that is basically for the less common tumors what you are really all talking about is developing at a preclinical level target identification which would justify the use of a pharmaceutical agent that will be coming out. And, I think the goal should be to get access to a drug irrespective of whether there is an adult counterpart, but basing the access of the drug on the need to address inhibition of a target.

I think that that approach needs to be utilized, but I would agree it is hard to imagine that the pharmaceutical industry would be willing to give you a drug that is, say, used in small cell or being developed for small cell carcinoma and you are going to mount a trial now in medulloblastoma where you are basically going to have to do Phase I, Phase II and everything. That probably should

be one of the major goals of this committee, to try to work out a way that makes it easier, maybe gives the pharmaceutical company some either regulatory or financial incentive to let that drug out for the use in pediatrics.

DR. PAZDUR: That is the whole pediatric plan that we developed under the FDAMA interpretation, our interpretation of FDAMA, which allows the development of drugs in the pediatric population in a Phase I population, and even if there is prohibitive toxicity, if there is a good faith attempt that a Phase I study is done, then they get the carrot of six months exclusivity attached to their entire product line. Likewise, if they do a Phase II study and it turns out negative, it is a good faith attempt in providing what we require as needed information so they do get that carrot. So, that has been built into the exclusivity plan for the development of pediatric drugs.

DR. SANTANA: Steven?

DR. HIRSCHFELD: Yes, I wanted to just address the matrix issue once more. Rather than necessarily thinking of a triad of investigators, regulators and industry, I want to emphasize a

matrix. And, there are many other components, most important patients and their families because they are the ones who are the focus of all our efforts, and many other people who have an interest in it. I think that we have made an attempt to engage in dialogue with as many people as we think have an interest or, as they are called fashionably these days, stakeholders in the problem, and I think it will require efforts which will involve all of us.

At the last meeting that we had our pharmaceutical industry colleagues had the opportunity to conference over lunch and make a statement after lunch, and I wouldn't necessarily want to put undue pressure if they want a little more time to consider some comments.

DR. SANTANA: Anthony, yes?

DR. ELIAS: Yes, I just wanted to talk about a different matrix of sorts because we are talking about what do you do with rare diseases. One of the other matrices, of course, is that now many of the tumors in adult oncology are going to be subdivided. They are going to be subdivided in major ways based on gene array and we are really going to be starting to talk about pathways, what pathways are important. So, you are going to have

maybe EGFR being an important pathway across multiple disease histologies and maybe you will have a drug that is going to be approved for any tumor that is EGFR, that has that as an important pathway.

Now, we also do know that some of these pathways may be different within the context of the cellular milieu but, nonetheless, I think we may be completely reorganizing our oncology taxonomy and really be talking about pathways, which pathways are important. I think that may completely shift the types of indications people are going to be looking for and make what was once a very rare tumor into something extremely common.

DR. SANTANA: Yes, I want to follow up on that. I think, you know, historically the agency and the sponsors seek an indication for a very specific item -- you know, second-line salvage therapy for metastatic breast cancer; that is the indication; that is where they come forth. I think what you are suggesting, and I think we have thought a lot about that, is that maybe it is time for all of us to rethink that; that there may be some drugs or some biologics in which the indication which the sponsor seeks and that the

agency is after is very different. It is not the historical, traditional breast cancer salvage therapy for metastatic disease, but maybe some biologic event which this particular target agent targets.

DR. PAZDUR: We welcome that, and we could handle that by labeling. For example, a drug could be approved if it inhibits this enzyme in a variety of tumors. So, that can be handled by labeling. So, that is not an insurmountable problem for us to overcome and basically apply to a pediatric situation if there are tumors in the pediatric population that overexpress that --

DR. SANTANA: Yes, the challenge is to identify those.

DR. PAZDUR: But this has to be well defined by the scientific community, that this is a way to reclassify tumors. Remember, whenever we are mandating a company to do something it is a little bit different than just saying, "won't you do it? It would be nice." This carries a stick with it and repercussions for the company both financially and from a regulatory point of view. So, we have to have a sound scientific basis. It can't be on the basis of one report or a feeling

that these tumors may overexpress this issue. It has to be a recognition that there is a change in the taxonomy of how we deal with these tumors and the terminology.

DR. SANTANA: Yes, Donna?

DR. PRZEPIORKA: To follow up on a comment that you made regarding labeling, using as an indication inhibition of a particular enzyme or pathway, would that be outside the context of doing a full study to determine whether or not that pathways in, as Anthony put it, the cellular milieu is actually going to be effective? Would you still not require a specific disease indication?

DR. PAZDUR: No.

DR. HIRSCHFELD: We may not.

[Slide]

I put up a slide, which I had in reserve, which shows the type of principle and it echoes the same thinking that Dr. Elias articulated which we have been discussing for several months, and which we have discussed in previous meetings of this committee. It states in sort of broad terms that if a lesion -- and we haven't stated what a lesion may be but it could be a pathway, a translocation, overexpression of a particular gene, point mutation

-- is necessary for establishing or maintaining the malignant phenotype, and if a therapy is directed against that lesion, then studies in tumors where the lesion occurs and has the same critical role are warranted. So, there are a number of conditions. It shouldn't just appear in cells but it must play some central role in the pathogenesis of the tumor type. That is the type of general thinking that we would like to be moving toward and away from the more conventional, historical, traditional approach.

DR. PAZDUR: But this is going to require a great deal of work obviously and, you know, I don't expect a sponsor to come in and say, "okay, this is a target and we're just going to develop the drug only in this target" because they are subject to basically the same confines as we are -- is this a well accepted change in the way physicians look at tumors?

How I would expect this to occur over time? Probably these targets will be identified in a particular tumor. When confidence develops that this is the way that the drug works, then this will be extended and we will kind of divest ourselves perhaps of the histological confirmation of tumors.

But I think it is going to be a multi-step process. It is not just going to be a bang -- this is the target and we will just develop drugs. I think it is going to be a step-wise evolution in how we look at things rather than a complete change in one study.

DR. HIRSCHFELD: And just one other point, our overriding and regulatory-derived principles must show patient benefit. So, the indication, I would expect, would never be for inhibition of EGFR in such-and-such a cell type. The indication would read for patient benefit for prolonging life in patients who have tumors that overexpress EGFR and have certain other characteristics, and all we would be doing is moving from a histologic description of the tumor to a more functional or biological description but it absolutely must show patient benefit.

DR. SANTANA: I think our colleagues from industry want to go ahead and make some comments. For the purpose of the record, please state your name and your affiliation.

DR. RACKOFF: I am Wayne Rackoff, a pediatric oncologist at Johnson & Johnson. I just wanted to make one comment and then Raj is going to

make a number of others, just to support what Steve said about the comment that Roger made about adverse events. This has come up, and I make this comment really as one of the co-chairs of the COG Industry Committee. It has come up in repeated conversations; it has come up in conversations with children's advocates and in our committee and here, and in the committee at COG it has come up and, Steve, we just want to support what you say, that there are no data that support that this has ever been an issue.

I think, just talking among ourselves especially with the number of pediatric oncologists who have entered clinical research and development within industry, it is not something that we hear a lot. There is always a concern, especially from our commercial counterparts, about how we will deal with toxicities in labeling and then in commercialization. But in research and development and in looking especially at the necessity of providing a clinical development plan for pediatrics when we come before the FDA, we know that there are pediatric oncologists within FDA who are sensitive to the issue that the labeling will have to reflect that a specific toxicity occurs

just in a subpopulation.

So, we hope that what Steve has said, and we will reiterate that over and over again at meetings as it comes up, that that is not and should not be a concern in inhibiting investigators, consumer advocates and families from coming to us and suggesting a study that would be appropriate in pediatrics.

DR. MALIK: I am Raj Malik, with Bristol Myers Squibb, also a pediatric oncologist. Just a couple of comments, and I am speaking on behalf of the COG Industry Advisory Council, and that has been a great forum for really establishing, I think, a new paradigm of collaboration between the COG, the NCI, CTAP, FDA, certainly patient advocates in terms of really addressing all the issues that are being discussed here.

I think one of the issues that was discussed at our last meeting was really the issue of prioritization, and I think it keeps on coming up over and over again because it speaks to, as Dr. Pazdur said, to the sound scientific rationale. It speaks to how are we going to take these 400 agents in development and pick up the best agents to develop in children. And, that is certainly a

process in which industry is also very interested in participating and I was very glad to hear from Dr. Smith that the first such meeting has already started and we, in industry, look forward to participating in that dialogue as well.

So, in general, you know, we are also very supportive of the efforts that are going on here and having a core of pediatric oncologists in industry right now I think makes for a very collaborative environment.

DR. SANTANA: Thank you for those very supportive comments. Yes?

DR. MELEMED: My name is Allen Melemed, with Eli Lilly. I just want to add one thing that wasn't stated. I hate to say this but we have somewhat of a bias because we are some of the larger pharmaceutical companies that are usually at these so there is somewhat of a resource issue from larger pharmaceuticals to smaller pharmaceuticals in the sense that we have more people, more pediatric oncologists in the company and they may not have the same resources to get the clinical trials, and they may not have the same resources as far as the actual drug supply. So, there is somewhat of a bias, obviously, with the larger

pharmaceuticals. So, it might be harder on the small biotechs where they have these new drugs that you want. So, that is one thing I wanted to say.

The other thing is the timing of the studies. The Pediatric Rule is a mandate. Now, the FDAMA is a bonus and an addition that you can get on exclusivity. That is a patent extension and that extension occurs at the end of the patent. So, you want and obviously we want pediatric oncology drugs now, but for FDAMA you can actually do studies at the end of the patent life or when the drug is already marketed. So, a lot of this doesn't address the incentive; it addresses the rule and that is why you have to be careful how you administer the rule.

DR. SANTANA: Anybody else have any comments? Malcolm?

DR. SMITH: I would have a question to Henry and others relating to the slide that Steve has put up. One of the slides mentioned a report of EGF receptor expression in the majority of pediatric gliomas but not the amplification of the gene. So, what data do we need then to say that this is a valid target for pediatric high grade gliomas or that it is just unrelated; it is there

but it is not really doing something, and how do we develop those data to inform us?

DR. FRIEDMAN: Specifically are you asking is the amplification going to be an issue or just the increased expression?

DR. SMITH: Well, that is my question.

DR. FRIEDMAN: Okay, what is the relevant parameter for a drug being effective, an EGFR inhibitor, for example, in this setting?

DR. SMITH: Right, how do we know? We know expression and what do we need to know to be more confident or to be confident that, in fact, an EGFR inhibitor would be a good drug to try in this population?

DR. FRIEDMAN: I think in any given situation the hope is going to be that there are trials being conducted to help answer that. In point of fact, for that particular question there are several trials, including one at Duke that specifically we will know in the space of 12-15 months what is the relevance of EGFR amplification wild type versus mutant and increased expression without amplification versus activity of an EGFR inhibitor. And, there will be studies like that I think from a number of different sources. I am not

sure if that is going to be happening, Howard, with you or not at NCI, but I think that as we get a better idea of what biological parameter, in this case expression versus amplification, is critical we will be able to have the answer to your question. For that particular question probably 15 months from now we will have the answer.

DR. SANTANA: Susan?

DR. COHN: Yes, I just wanted also to follow up. Malcolm, I think the meeting that you had yesterday, looking at these preclinical models, is certainly one thing that we will be very interested in looking at and seeing if that will correlate. So, I am sure it will be relatively simple to set up some preclinical models looking at EGFR expression versus amplification and then looking at efficacy of various targets to see if these models respond or don't respond. I would imagine that would be certainly a place to start in terms of prioritizing.

DR. LEVIN: If I may make a comment, I don't think it is so simple because the issue with some of these new molecules is to understand how to use them. I, for one, would say that it doesn't make much sense to give one of these inhibitors for

an amplified target like EGFR because you have the issue of conservation of mass. You have to knock down too many receptor tyrosine kinase sites than you can possibly do.

I think that a lot of the preclinical research done by industry and, hopefully, done by pediatric consortia and private academic institutions has to address the issue of, one, is the target really good; two, what is the optimum dose of these agents that needs to be given to inhibit the target, not what is the optimum dose to be given to produce the toxicity, the MTD that will then allow you to go forward. We need to understand exactly how these drugs work in order to use them well, and I think it is going to continue to be increasingly the goal of most successful pharmaceutical efforts and academic efforts to learn how to use these drugs so that they can be used in combination. I think that is going to require a commitment from industry, academia and the NIH. I do not think that the commitment need come from the FDA.

DR. FINE: To echo that and to follow up on the meeting that we had yesterday on the preclinical model, I would propose that that is

really the challenge to the pediatric academic community. If they want to have the Pediatric Rule more commonly come into play for access to better drugs, the onus is on us to actually show that these targets for these new drugs are validated targets for pediatric brain tumors and that the preclinical data supports their use, at which point then the Pediatric Rule simply comes into play. I am not sure it is necessarily the onus of the pharmaceutical industry to do that. So, if we want drugs for our children, I think it is within the academic community to make that preclinical data come to fruition.

DR. WEINER: From the parents' and patients' perspective, I think what we really want is reassurance that the science will prevail regardless of either the economic incentives or disincentives or regulatory environment. When we bring our kids into the clinic, it is the trust that the science will dictate those decisions rather than any other consideration and I think it is absolutely imperative that that is what prevails in this environment.

DR. SANTANA: Very appropriate comment.

DR. POMEROY: I think another aspect of

this that may be driven as we understand tumors better actually has applied to histologically based taxonomy of tumors as well, which is that there are some tumors, such as glioblastomas and high grade gliomas, that are very prevalent in adults where the development of treatments is very rapid and, yet, they are very rare in children. So, we end up, because of a numbers problem, not being able to conduct trials at the same pace.

I guess one question that will be raised, as we have these new inhibitor compounds and a new understanding at a molecular level of what is going on in these tumors, is are there ways that we could apply either statistically or by joint trials an efficacy trial which I think we all agree, at least I certainly agree, is the big issue for many pediatric brain tumors, more than toxicity. How can we include children in trials that move along quickly so when a new compound comes along we don't have to wait five years to test it? Because I think things are going to be moving along pretty quickly over the next ten years.

DR. SANTANA: Anthony?

DR. ELIAS: Yes, I would agree with Howard. I certainly don't think that the science

is yet there to be able to say that, for example, any time you see EGFR that is going to be an important pathway. I think our experience, for example, with anti-ras therapy with FCI is just a humbling case where it probably is the case that, in fact, the targets that we are targeting are actually not perhaps the targets that actually will work.

So, I think to a certain extent the principle of developing things where EGFR is, in fact, an important target or one other pathway is an important target across histologies is at least plausible. I think we are not there yet to be able to know what the gene patterns are, the milieu and so forth to be able to predict yet without actually testing it. In the future the hope will be that, in fact, certain gene patterns are going to be able to predict for response to certain types of interventions and that you will be able to tell but I don't think we are quite there yet.

DR. SANTANA: Robert?

DR. BENJAMIN: I would like to echo what Scott said from a sarcoma point of view. If we try to deal with specific pediatric studies in specific sarcomas, whether defined based on a molecular

abnormality or defined based on histology, there will never be enough children to study. Therefore, if a separate study needs to be done the children will never get the drug. I think the alternative strategy, which is really not addressed by the rules as I see them, is allowing for participation of human beings in studies of their cancers regardless of their age. I think that would allow children to get their drugs more quickly when it is appropriate.

DR. HIRSCHFELD: I think we recognize that and on a to be announced date we will specifically look at that issue of trial design and trial access.

DR. SANTANA: Roger?

DR. PACKER: I would certainly echo your comments as long as we set up those studies, and this goes back to trial design, to know what we are monitoring; that we can't always be monitoring the same things, such as lowering of blood count or elevation of liver functions. If you are going to be monitoring aspects of brain development and brain function differently in that population, I am certain on board with that.

I would still like to come back to that

principle that is up there, and the term that really keeps jumping out at me is "malignant phenotype." We are still missing a large grouping of patients and if we are going to be basing things, as we say, on a biologic basis and this receptor or this chemical being elevated in the specimen we are again going to be treating patients relatively late in the course of their illness.

One of the other things that I would like this committee to battle with and the FDA to help us to work with industry is how do we apply these things, again, at a time where they might be more effective -- going back to Dr. Levin's comments -- not only in pediatrics but in adults at a time when the tumor has not mutated to GBM, where we may have not picked up the same markers and where we may not have strong biological rationalizations, except the clinical story will tell us that if we have a low toxicity molecule maybe we should apply it early in the course where we don't have compelling data yet that things are amplified? That is where I don't see these models helping us dramatically in getting that early application.

DR. LEVIN: I think you have to be a little careful though because we should be the same

as industry in some ways and we should be focusing on the target. So, say, for the lower grade tumors you find a set of target molecules, you should really be seeking your drug based on that. Some of the molecules that are out there, for instance EGF receptor inhibitors, might well work much, much better in that subpopulation. So, it is going to be up to somebody in academia to come forward with a hypothesis that says I can test this in animal systems or I can test it in cells, and it appears as if this is more likely to be effective in the subpopulation, therefore, I want access to the drug to test it against that population. The pharmaceutical company might say, well, there are only 50 patients a year with that disease; it doesn't financially pay, and what you are really asking then is, is there another mechanism by which you can get access to that chemical.

DR. PACKER: Let me just comment on that one other time. We have talked about a transformation of tumors from low grade to high grade and that has already been presented. There is a point in all of these tumors, we think, especially as they march along to glioblastoma multiforme, where they picked up some of their

transformation but maybe it is not high enough that we have been able to pick it up in a Petri dish. Those molecules may be extremely effective when there is a very low amplification, and if we are going to be stuck and have to wait until we can prove that we are going to miss the opportunity to impact on the disease early in the course, and we do a very bad job on impacting on disease later in the course and although these molecules may be wonderful, nothing yet has proved to me that when disease is rampant it is going to turn the disease off. And, I just want to know how to get at it not only early in a patient population but early in the course of the illness to the patient.

DR. HIRSCHFELD: I would like to ask Dr. Poplack if he could just address this because I know he has thought very much about this, and there are in the hematological malignancies conditions which are called preleukemic states and I would like you to make a comment as to whether therapy or intervening in these preleukemic states has thus far had any impact, or just how you would approach the problem.

DR. POPLACK: I think that there is certainly a need to apply therapy in some of the

preleukemic states. I am not sure whether we have analogies in brain tumors that would be appropriate for therapy, and I think probably appropriately we are focusing on the situations of greatest need. Whatever principle we adhere to or gets applied needs to be assessed and proven through these trials, and I think it would be more difficult, Roger, for us to be applying therapies to suspected or hypothetical situations where we don't have biological evidence even if there is a need. So, I am not sure how you would suggest that we would apply an agent, without having biological data, just because there is a need.

DR. SANTANA: Yes, and the challenge to identify those populations because you are now going to be targeting populations that don't have the complete spectrum of the disease. You are targeting at a very much earlier point and the challenge is to be very careful to identify those populations.

DR. PRZEPIORKA: In the hematologic group I think the one example that comes to my mind, because of recent action, is Gleevec where the tyrosine kinase inhibitor works wonderfully in the chronic phase of CML which we don't consider

potentially a full malignancy, but doesn't work anywhere near as well in blast crisis when there are so many other things that actually contribute to the malignant phenotype. The challenge, as Victor put it, is trying to identify what is going to be important early on, and studying the malignant cells will give us a whole array of possibilities but we have to figure out what is that one thing that early on we can step in there and really deal with.

I just wanted to make one additional comment. I think in planning the drug design meeting it is important to think about the public health interest in making sure the drugs are available also in adults with diseases that are prevalent in small numbers, the same way that we do with the pediatric groups.

DR. SANTANA: Dave?

DR. PARHAM: I think one thing we are going to have to come to grips with in this discussion is that in the groups of neoplasms we are discussing there is no analogy to preleukemia. All of these tumors develop in a full-blown malignant fashion, particularly in sarcomas. Even in the brain tumors fibrillary astrocytomas are

very, very uncommon and by the time they announce themselves as tumors they are full-blown malignancies or else they are pilocytic astrocytomas which very rarely later on develop a malignant phenotype. So, I am not sure that discussion is going to be helpful here because there are no identified pre-malignant stages in these tumors.

DR. SANTANA: Good. I am going to go ahead and ask that we take a break. We have had a very good discussion. Let me summarize two points in very general terms that I perceived from the discussion this morning with a lot of detail. One, I think through this whole discussion through all these meetings, it is important, like somebody has reminded us, that the endpoints don't change whether we are talking about the Pediatric Rule or any other mandate. We are still looking at bringing forth treatments that are scientifically based with a good rationale and that ultimately demonstrate some efficacy and some benefit for the patients. So, I think that is a central point in this discussion.

The second thing that I think is very important to recognize is that it is encouraging to

hear that both the agency and other federal agencies that deal with pediatric oncology and sponsors are willing to start thinking outside of the famous box in developing probably other models with some of these new biologics and some new principles that potentially could apply. So, it is very encouraging to hear that we are moving into a different phase and that the agency is willing to consider these proposals in a very different way.

I think we have talked about the general things this morning. After the break we will specifically start addressing some tumor types. So, let's go ahead and take a 15-minute break and reconvene at 10:15. Thank you.

[Brief recess]

DR. SANTANA: We are going to go from the general now to the specifics. The first session in which we are going to try to address issues is on sarcomas. Before we get started, I am going to ask Karen to just briefly give us some instructions about lunch. Then after that, any members who joined us after we started this morning do need to introduce themselves for the public record. So, I will ask those of you who came a little bit late who did not introduce yourselves this morning to do

that. Karen?

DR. TEMPLETON-SOMERS: We have made arrangements for those of you at the table to be allowed into the Parklawn Building. So, you can pretend you are a regular federal employee and eat in our cafeteria, which is the most convenient place. You are not obligated to go there but it is quick --

DR. SANTANA: It is an honor!

[Laughter]

DR. TEMPLETON-SOMERS: It is an honor, yes! Victor has been there before and he is willing to go back.

DR. SANTANA: Stick with the salads!

[Laughter]

So, when we are done with the morning session we will just walk over there and Karen has arranged for some stickers because we have to go through security over there too.

Any committee members that joined us late, could you please introduce yourself for the public record by stating your name and affiliation?

DR. KAYE: Frederic Kaye, from Centers of Cancer Research, NCI and the Naval Hospital.

DR. SANTANA: Thank you.

MS. KEENE: Nancy Keene.

DR. SANTANA: Patient. Thank you, Nancy. We are going to get started. Our first presentation is by Mike Link, from Stanford. Mike?

Perspectives on Sarcoma

DR. LINK: Well, first I would like to thank the committee. I am flattered to be asked to speak here and, as I understood my charge, which I may not have understood, I was going to give some perspective on sarcomas to set the tone for some discussion.

[Slide]

As such, I will give a brief tour of the sarcomas to provide some background at least from the pediatric perspective. I talked with Bob before and I hope that he will fill out those aspects that we don't like to deal with.

[Slide]

So, I am going to give you some themes. This is not the conclusion slide, this is the themes, sort of the punch line that I might as well get to right at the start. First of all, sarcomas are a heterogeneous collection of diseases and families of diseases so that we shouldn't be thinking of them as a group.

The individual diseases and families may be defined molecularly and a molecular derangement characterizes each tumor type usually so that in the ones where it has been explored there is often a particular molecular derangement which defines the malignancy, and this derangement in most of our minds, even if not in minds of all pathologists, supersedes system morphology in defining the disease. So, we are now defining the disease on a molecular basis.

It is unlikely, however, that the characteristic molecular derangement is the entire story. So, obviously, one molecular derangement doesn't make a summer, to paraphrase that, and I think obviously we are learning from further gene array studies that there is a lot more that goes on beyond the initial event.

But one thing that is important for this particular discussion is that I think that these are prototypic diseases which span the child and young adult age range. So, this is a disease of children and young adults and so obvious for this particular kind of discussion.

[Slide]

From that, I am just going to proceed to

the usual background talk. This is a small piece of the action in children as it is in adults. So, it is only those red things, about 11 percent of all the tumors we are talking about are the soft tissue and bone sarcomas.

[Slide]

The way that I think most pediatricians think of them, although I will be glad to be corrected by others in the room, is that we divide them into essentially three groups of tumors, three major groups, the osteosarcoma; the Ewing's family of tumors which is bone and soft tissue tumor and includes peripheral primitive neuroepidermal tumors and others, and I will go into that to show you that this is a family of tumors that has now been unified by a molecular concept; and then a group of tumors that has been disunited perhaps by every factor that we can think of, the soft tissue sarcomas, the non-rhabdomyosarcoma soft tissue sarcomas, about which I will have very little to say, relying on Bob for that; and rhabdomyosarcoma which we know is heterogeneous in itself because it includes embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma which, I will show you, are very different diseases even though we treat them with

the same treatment strategies, and other variants which are probably less important because they are very rare.

[Slide]

I do want to leave you the impression that we have made progress in these diseases and, in fact, some of the progress that we have made is one of the problems in terms of new drug development. This is the history of, let's say, the overall five-year survival in the three major groups of sarcomas, rhabdomyosarcoma, osteosarcoma and Ewing's sarcoma which appear in childhood. This was in an article in The New England Journal of Medicine showing progress over time. As you can see, with the current state of the art there are, fortunately, fewer patients left who are candidates for experimental therapies at least as front-line treatment.

[Slide]

I am going to start with osteosarcoma and not say too much about it because Bob Benjamin is also an expert here, but I just wanted to demonstrate that age of onset of the disease probably tells the story, more than anything better, why this is a disease that adults and

pediatric patients should be considered together. As has been stated before, I don't know that there is much difference between a child in the second decade or an adult in the third decade of life in the behavior of the disease, assuming that we are talking about classic osteosarcoma.

[Slide]

There are some molecular derangements in osteosarcoma, although I think that most of us would agree that not a single one of them unifies the disease in the way that I will show you for the other sarcomas, but there are mutations in RB gene and p53 mutations which are certainly characteristic of a minority of patients; MDM2 amplification and, through this, inactivation of p53 which occurs in a minority of patients and overexpression of Her2 which is an important therapeutic target, but not in all patients. I think, again, no single molecular derangement defines this group of diseases.

[Slide]

I understood that I was supposed to give you the state of the art or the state of the therapies that we have and I am going to give you two slides which show the unfortunate circumstance,

as we talked about earlier, where we are able to do perhaps in the best of circumstances a trial every four to five years. We haven't necessarily always been able to accomplish that but even when we have, this is the outcome of a trial that I ran between 1981 and 1986 with a long-term event-free survival of somewhere in the neighborhood of 57 percent but a 4-year event-free survival, as you can see, of somewhere near 60-some percent.

[Slide]

Then a trial that Paul Meyers, who I am sitting next to, just finished running, from 1993 to 1997 and the overall outcome is pretty much superimposable on the curves that I just showed you. So, a couple of decades of work and not much progress in terms of the number of patients that are cured.

[Slide]

A group of patients who we also have not made much progress against is patients with metastatic disease. Staging of bone tumors is pretty easy. They either have metastases or they don't that are clinically evident. This is a group of patients where about 20 percent of them are cured. They fare poorly even with modern

treatments and are, obviously, appropriate candidates for new approaches as first-line therapy.

[Slide]

Now I am going to turn to the second category, Ewing's sarcoma, similarly a disease of young adults and children but where the curve is shifted dramatically more to the left. So, I think that most of the adult oncologists would agree that we probably know more about it or at least have more experience with it than our adult oncology colleagues.

[Slide]

Here we have the first of a group of diseases where there is a molecular derangement which characterizes the disease and underpins tumorigenesis. Ewing's family of tumors is characterized on the right, as you can see, with a chromosomal translocation between chromosomes 11 and 22 usually, which produces a fusion gene and gene product which characterizes about 95 percent of cases of Ewing's sarcoma in the tumor cells, and is felt to be a felt and malignant transformation. On the left you see an analogous transformation which I will return to in discussing alveolar

rhabdomyosarcoma.

[Slide]

So, this is a reciprocal translocation found consistently in all of the family of Ewing's sarcomas. So, soft tissue Ewing's, PNETs tumors, all of the diseases that have had various different names but now are unified together. Through EWS is fused FLY1 or ERG, the two common partner genes, and this translocation results in a tumor-associated fusion gene which can be detected by a variety of techniques in virtually all cases and, therefore, has become sort of a diagnostic test which we use to diagnose the malignancy often more rapidly than we can get an answer from our pathologists.

[Slide]

What is the state of the art? Again, about two-thirds of the patients with no evidence of metastatic disease are cured compared to patients presenting with metastases that are overt where somewhere in the neighborhood of 20-15 percent of the patients are cured. Again, the same theme as I said for osteosarcoma, a group of patients where we need better approaches.

[Slide]

But there are some confounding variables. This is a site-specific tumor. Patients with certain sites do better than others. I am not going to show all of them here but there are obviously confounding variables in this related to tumor size and presence of metastases, etc. which contribute to this, but they have to be considered separately and is one of the caveats when we talk about just lumping patients together.

[Slide]

Here is another theme that will recur, although we think they are the same diseases, I believe, in older patients and younger patients, but there is a theme where, again, younger patients do better. Children less than nine years of age fare significantly better than older adolescents and young adults. I will get back to this -- I don't know if it qualifies as one of the pitfalls but is certainly one of the caveats that we have to think about in terms of lumping tumors in older patients and younger patients together even if they have the same molecular underpinning.

[Slide]

Now, the soft tissue sarcomas -- rhabdomyosarcoma is the most common soft tissue

sarcoma in children.

[Slide]

More so than even Ewing's sarcoma, this is a disease of young children, although I don't know if it shows up on this slide. Part of the problem with this slide, of course, is that many of the studies of rhabdomyosarcoma entered patients for a while only up until age 21. So, I am not sure that we really know what the incidence is. There are clearly a lot of young adults out there with rhabdomyosarcoma but they have not appeared on clinical trials so they are essentially lost to us in terms of understanding them very well. But here you can see that the majority of kids are presenting younger than age nine, and certainly the overwhelming majority younger than age 15.

[Slide]

Here it is very clear that this is at least two diseases, even just by histomorphology and we know that there is an alveolar and embryonal subtype. Although until now most of the principles of therapy have been shared between the two, it is pretty clear that these two diseases are quite different, and it is not necessarily clear why we lump them except that because of the problems of

limited numbers of patients we often do so for convenience and to get more robust clinical numbers for our trials.

But it is important, as you can see if you look at the BOTR, which is a botryoid which is another version of embryonal, and lump that yellow curve with the green curve which is embryonal and then compare that to the lowest curve, the gold curve, which is the alveolar histology, you can see that this is really a very significant difference in outcome depending on histology. So, it is an important difference clinically.

[Slide]

Of course, as I have shown you, the alveolar variant is associated with a chromosomal translocation and the production of a fusion gene unique to alveolar rhabdomyosarcoma.

[Slide]

If you look at the lower half of this slide, this translocation, 2:13, is similar or analogous to Ewing's sarcoma fusion gene, PAX3 to one of the fork-head transcription factor members, and there is an infrequent similar translocation that involves PAX7 and FKHR, which I will talk about in a minute. So, there are two very, very

similar translocations which characterize alveolar rhabdomyosarcoma, and there are some cases that don't have or at least have no detectable translocation at all -- very different from embryonal rhabdomyosarcoma where certainly no clear-cut gene has been identified that characterizes the disease.

[Slide]

Now, even the difference in the translocation has an impact on the outcome of the patients. So, the more common PAX3 involved, the orange curve -- if we just look at patients with metastatic disease, those patients fare terribly, whereas those that have the alternative translocation involving PAX7 actually do quite well. So, again, we have to be very careful in terms of defining the disease based on a fusion gene because we think has variations in the fusion gene do make a difference. I think, although it is not entirely clear that everybody believes it but in the Ewing's sarcoma there are variants of the translocation and it seems that different break points in translocation are associated with more favorable or less favorable outcomes.

[Slide]

Once again, we have made progress overall in rhabdomyosarcoma but when we look at how we are doing lately it is pretty much the same, about 65-70 percent of children presenting with non-metastatic rhabdomyosarcoma are cured, although in the results of our last study, which was published just recently in The Journal of Clinical Oncology, there is no difference in outcome. When we use three different regimens all of the drugs have activity but there is no improvement in outcome by regimen.

[Slide]

Now, rhabdomyosarcoma is a disease that is unique in one way, and that is the disease behaves very differently depending on the site of involvement, and this makes one of the difficulties in talking to adult counterparts where they have site-specific diseases like breast cancer or bowel cancer. This is a different disease at any of the sites and it occurs in a multitude of sites.

[Slide]

If you look at the outcome by site, and I am not going to belabor each of these things but you can see that the outcome varies from 90 percent, the top curve, to more like 60 percent for

other presentations and this putatively is the same disease. So, again, we have the problem that although we think we know how to define this disease, it is very different in its behavior depending on a number of different factors.

[Slide]

Then, a recurrence of this theme in terms of the impact of age, we know that older patients do less well, as I will show you, and part of the reason for that is because if you look at the incidence of alveolar rhabdomyosarcoma, which I have shown you is an adverse prognostic factor, the incidence of alveolar is higher in older children, 33 percent for example in children older than 10 years of age compared to only 18 percent in children in the 1-9 age group. So, a highly significant difference.

[Slide]

Even stage of presentation -- older kids much more frequently present with advanced stage disease, again accounting for why older children may do less well.

[Slide]

If we summarize what happens in older kids with rhabdomyosarcoma, they have a lot of things

that make them less favorable which may or may not have to do with the underlying biology of the tumors that occur in older children. So, they more frequently have alveolar tumors; tumors arising in extremity, which is a bad site; larger tumors; more invasive tumors; more regional spread and more metastatic spread. So, not surprisingly, they do less well. So, the question is, is this a feature of a different disease in older children or are there really fundamental biological differences, analogous to some of the things we saw in brain tumors that Henry showed?

[Slide]

This is just to demonstrate the relapse hazard. So, the lower this curve, the better the patients do. As you can see, it goes up both in very young children and older children, showing that those patients are much more at risk to relapse.

[Slide]

Now I am just going to make a brief foray into an area where I know very little, and most pediatricians don't know very much and I hope Bob will talk more about these, but when we talk about the soft tissue sarcomas of children and you take

out rhabdomyosarcoma and its variants and soft tissue versions of the Ewing's family of tumor, we are left with just a long list. I think Bob's is longer than mine, but these are the ones that occur in children and they are very, very heterogeneous in their histologic appearance, their behavior, etc., but the common ones that we see are synovial sarcoma. The ones I want you to focus on are -- it is not even up there, but a couple of the others that are important and I will show you the reason in the next couple of slides.

[Slide]

The reason is that similar to Ewing's PNET and alveolar rhabdomyosarcoma, some of these soft tissue sarcomas are now also molecularly definable. So, we can group them. For example, desmoplastic small round cell tumor, characteristic translocation, characteristic genes involved and, actually, they are kind of familiar because the EWS gene is involved in this tumor as well although fused to another partner, Wilm's tumor gene, so another pediatric partner is chosen. Similarly, synovial sarcoma and congenital fibrosarcoma also have very characteristic translocations -- again, titillating in terms of the fact that we can define

the diseases and also have a potential target for intervention.

[Slide]

My last slide on soft tissue sarcoma, just to show that, number one, children without metastases do very well; number two, that interventions beyond surgery and radiation therapy haven't made much of an impact that we know about. I suspect there has been some impact overall in adults but for a pediatrician it would be difficult to be convincing, although it may be convincing to an adult oncologist. The differences are quite small.

[Slide]

So, having said all that, what are the considerations when we try to link pediatric and adult patients with sarcomas? We can say that the diseases occur in children, adolescents and young adults, excluding, let's say, the non-rhabdomyosarcoma, the soft tissue sarcomas which occur in older adults as well, but these are basically diseases in a group of patients which span the adult and pediatric ages.

I think we could say that the diseases in adults and children may be similar on a molecular

level. I don't think there is any evidence that adults, at least for the fundamental translocations, have a different translocation but there is obvious heterogeneity even within each of these major subclasses of sarcomas, even histologically, biologically. There are different outcomes. And, it is pretty clear that there are other significant molecular derangements and differences in gene expression which will be likely to be determined, if they haven't already been determined, which distinguish patients even within a category and probably older patients from younger patients.

[Slide]

What are some of the other considerations? Well, as you have heard in the talks in this session, there are limited numbers of patients available to begin with. There are hundreds of patients with these tumors, not thousands of patients each year in the United States newly diagnosed. We cure a relatively high proportion of them with current therapy so that there is limitation on what subjects are available for experimental therapies. Not to say that we wouldn't be interested in incorporating an

experimental therapy, but it does make it difficult to try to decide how you are going to cut back on what we know is curative for two-thirds of the patients. Therefore, it seems obvious that we should be combining efforts among adult and pediatric patients where the disease really appears to be a continuum encompassing pediatric and adult patients.

[Slide]

So, what are some of the other problems? Older patients fare less well in all varieties of sarcoma virtually. How do you explain that? Well, are there really true age-related biological differences? In other words, are older age patients associated with other features of the tumor itself that may not be defined by the primary translocation but other molecules that have yet to be defined that may be different in older patients and younger? It wouldn't be surprising.

Age remains independently prognostic in the studies that I have shown you. This may be also a reflection of host tolerance to therapy. So, it is a difference in host rather than difference in tumor. It may be a difference in compliance with intensive therapy. We know that

improvements in outcome have resulted from therapies which are pretty hard to give and if you had a choice, which a child may not often have, they may not always come in on time. And, there may be differences in physician compliance with intensive therapy.

So, it is not even a patient or a tumor issue; it is a doctor issue, and the mind set of a medical versus a pediatric oncologist, perhaps best demonstrated in a trial of treating adolescents with leukemia and the difference in results in a pediatric trial or a cooperative group trial that was presented at ASH in December are very compelling results, which showed very, very different outcomes, probably a difference resulting from doctor rather than fundamental biologic differences in the tumors.

[Slide]

I just wanted to conclude. So, these molecules that we have seen, and some of them kind of not primary targets for the therapies that have been developed, certainly present themselves as things that we ought to be interested in. For example, osteosarcoma -- Her2 is expressed and in those tumors Herceptin would seem to be a logical

potential intervention, not something that was developed with osteosarcoma in mind. The PDGF signal transduction pathway is blockaded by STI-571, again not a primary reason for the development of the drug but a reason to test it in osteosarcoma. Of course, for those tumors that have p53 and RB abnormalities, those might be suitable targets.

In rhabdomyosarcoma the fusion genes would be an interesting target either from immunologic approaches or from small molecule approaches. A similar case could be made for the Ewing's family of tumors and its specific characteristic translocation, and also in Ewing's the stem cell factor c-Kit signal transduction pathway could be blockaded by STI, again another application of a drug not developed specifically for that.

Desmoplastic small round cell tumor is not exactly a public health menace but it is a pretty nasty thing if you have it. Again, PDGF is putatively expressed in these tumors and might be a target for STI. I showed you some of the fusion genes involved in some of the other soft tissue sarcomas which we obviously be potential targets for new therapies.

Hopefully, I have given some of the reasons why we should be thinking in terms of unifying these but understanding, of course, that there are differences in adults and children and their outcomes which may present not necessarily obstacles but just food for thought before we can willy-nilly make the recommendation that these should be combined.

DR. SANTANA: Thanks, Mike. We will hold questions until we have the second presentation. I am going to invite Dr. Benjamin, from M.D. Anderson.

Perspectives and Background

DR. BENJAMIN: I use a Mac, which is intuitively obvious rather than this machine which is not.

[Slide]

This is just a picture of M.D. Anderson.

[Slide]

I am going to talk to you a little bit about the adult soft tissue sarcomas. Mike and I did talk in the beginning and I thought that, rather than overlapping, I would give you a very different perspective, and my perspective is that everything that you are talking about for

pediatrics applies in spades to sarcomas in adults. So, the question is how do you define these tumors? Should they be defined by patient age, histologic type, molecular abnormalities or whatever?

[Slide]

Sarcomas are extraordinarily rare tumors, less than one percent of all malignancies. Mike's slide showed you that it is about 10 percent of pediatric malignancies, so a higher proportion but smaller numbers. And, it is the smaller numbers that really kills us in terms of progressing in terms of knowledge in the treatment of these diseases.

I made the comment once that you wouldn't treat adenocarcinomas all the same way, would you? And, that came back to haunt me at a meeting that I was at in Europe, but no medical oncologist would think of treating adenocarcinoma of the breast the same way as adenocarcinoma of the colon. They are totally different diseases. Yet, if you asked people about treating soft tissue sarcomas, they are one disease.

[Slide]

Well, here is the one disease; there are probably 50. In fact, there has never been a study

which has adequately addressed the diversity within soft tissue sarcomas in adults, let alone put in the pediatric counterpart. Now, what was just presented to you very elegantly by Mike Link is that the pediatricians have done studies in osteosarcoma, single disease -- group of diseases but single group. They have done studies in the Ewing's family of tumors, relatively homogeneous group. They have done studies in rhabdomyosarcomas, some heterogeneity but relatively homogeneous group. The rest of the studies, the studies in adults are all done in "soft tissue sarcomas" and there are 25 different varieties or 50, depending on how you define them on a histologic level, not even at a molecular level.

[Slide]

You have already seen an updated version on this. Many tumors do have specific translocations. The ones in the pediatric age group tend to have more, but I can point out for you myxoid liposarcoma, which is a disease which is almost exclusively an adult disease but which has a specific translocation; synovial sarcomas which occur certainly more frequently in adults;